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Burden of major gastrointestinal bleeding among oral anticoagulant-treated non-valvular atrial fibrillation patients

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Abstract

Background: Gastrointestinal (GI) bleeding is the most common type of major bleeding associated with oral anticoagulant (OAC) treatment. Patients with major bleeding are at an increased risk of a stroke if an OAC is not reinitiated.

Methods: Non-valvular atrial fibrillation (NVAF) patients initiating OACs were identified from the *Centers for Medicare and Medicaid Services* (*CMS*) Medicare data and four US commercial claims databases. Patients who had a major GI bleeding event (hospitalization with primary diagnosis of GI bleeding) while on an OAC were selected. A control cohort of patients without a major GI bleed during OAC treatment was matched to major GI bleeding patients using propensity scores. Stroke/systemic embolism (SE), major bleeding, and mortality (in the CMS population) were examined using Cox proportional hazards models with robust sandwich estimates.

Results: A total of 15,888 patients with major GI bleeding and 833,052 patients without major GI bleeding were included in the study. Within 90 days of the major GI bleed, 58% of patients discontinued the initial OAC treatment. Patients with a major GI bleed had a higher risk of stroke/SE [hazard ratio (HR): 1.57, 95% confidence interval (CI): 1.42–1.74], major bleeding (HR: 2.79, 95% CI: 2.64–2.95), and all-cause mortality (HR: 1.29, 95% CI: 1.23–1.36) than patients without a major GI bleed.

Conclusion: Patients with a major GI bleed on OAC had a high rate of OAC discontinuation and significantly higher risk of stroke/SE, major bleeding, and mortality after hospital discharge than those without. Effective management strategies are needed for patients with risk factors for major GI bleeding.

Keywords: atrial fibrillation, gastrointestinal bleeding, major bleeding, oral anticoagulants, stroke

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Correspondence to:
Steve Deitelzweig
Department of Hospital Medicine, Ochsner Clinic Foundation, New Orleans, LA, USA and The University of Queensland School of Medicine, Ochsner Clinical School, 1514 Jefferson Highway, 11th Floor – Hospital Medicine Ochsner Health System, New Orleans, LA 70121, USA
sdeitelzweig@ochsner.org

Allison Keshishian
STATinMED Research, Health Economics and Outcomes Research, Ann Arbor, MI, USA

New York City College of Technology, City University of New York, New York, NY, USA

Amiee Kang
Amol D. Dhamane
Neeraja Balachander
Lisa Rosenblatt
Jenny Jiang
Bristol-Myers Squibb Company, Lawrenceville, NJ, USA

Xuemei Luo
Pfizer, Inc., Groton, CT, USA

Jack Mardekian
Pfizer, Inc., New York, NY, USA

Huseyin Yuce
New York City College of Technology, City University of New York, New York, NY, USA

Gregory Y. H. Lip
Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, UK; and Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

Introduction

Atrial fibrillation (AF) is a medical condition characterized by chaotic and irregular electrical activity in the heart's upper chamber; it is the most common heart dysrhythmia diagnosed in the United States, affecting 3–5 million individuals.[1,2] Both vitamin K antagonists (VKAs), such as warfarin, and non-VKA oral anticoagulants (NOACs), including apixaban, dabigatran, edoxaban, and rivaroxaban, are used in stroke prevention among patients with AF.[3,4] Comparing efficacy and safety profiles across all oral anticoagulants (OACs) is challenging since the populations included in the pivotal clinical trials remain heterogenous. However, the increased risk of bleeding is a major concern with all OAC treatments.[5]

Gastrointestinal (GI) bleeding is the most common type of bleeding among OAC-treated nonvalvular AF (NVAF) patients, and it causes considerable morbidity and mortality (5–15%), which leads to significant health care burden;[6,7] major GI bleeding events occurring after OAC treatment initiation have been associated with significant 30-day mortality, hospitalization, and health care resource utilization.[8] A meta-analysis of landmark randomized clinical trials (RCTs) showed that, as compared with warfarin, while NOACs as a class reduce stroke or systemic embolism (SE) events by 19% and intracranial hemorrhage (ICH) by 52%, each NOAC varies in risk of GI bleeding.[4]

NOACs showed varying comparative risk of GI bleeding relative to warfarin in the RCTs. In the ARISTOTLE trial, apixaban had similar risk of GI bleeding compared with warfarin.[9] In the RE-LY trial, dabigatran administered at a dose of 150 mg BID was associated with a higher risk of GI bleeding [relative risk: 1.50, 95% confidence interval (CI): 1.19–1.89] and 110 mg BID was associated with a non-significantly different risk of GI bleeding (relative risk: 1.10, 95% CI: 0.86–1.41) compared with warfarin.[10] In the ROCKET AF trial, major bleeding from a GI site was more common in the rivaroxaban group (3.2%) as compared with the warfarin group (2.2%).[11] The ENGAGE AF-TIMI trial provided evidence that low-dose (30 mg) edoxaban was associated with a lower risk of GI major bleeding by nearly 33%, but high-dose edoxaban (60 mg) increased the risk of GI bleeding by 23% as compared with warfarin.[12] The 2016 European Society of Cardiology (ESC) guidelines for the management of AF recommended that patients with high risk of GI bleeding select a VKA or another NOAC over dabigatran 150 mg BID, rivaroxaban 20 mg QD, or edoxaban 60 mg QD.[13]

The common sites of GI bleeding differ according to specific OACs.[14–16] For example, while upper GI bleeding predominates in warfarin, 53% lower GI bleeding was observed in dabigatran users with a major GI bleed; for apixaban and rivaroxaban, upper GI bleeding is more common than lower GI bleeding (apixaban: 63% *versus* 37%; rivaroxaban: 76% *versus* 24%); and edoxaban showed comparable risks of upper and lower GI bleeding.[9,12,17,18]

Due to the increased risk of bleeding, many patients stop OAC treatment after a bleed.[19,20] For patients who have a major bleeding event, the ESC guidelines recommend re-initiation of an OAC as soon as the cardiovascular thrombotic risks associated with discontinuation are thought to outweigh the risk of subsequent bleeding.[13,21] If an OAC was not reinitiated after a major GI bleed, patients incurred similar or lower risks of recurrent GI bleeding events but higher risk of thromboembolic events.[19,20] Although the benefits of restarting an OAC have been found to outweigh the risk of bleeding, 25–50% of patients still do not resume an OAC after a GI bleed.[19,20]

There are limited data regarding OAC use and GI bleeding in the real-world clinical setting. In this study, we used pooled data of five US claims databases to examine the risk of stroke/SE and subsequent major bleeding between OAC-treated NVAF patients with and without a major GI bleeding event. Second, we analyzed event characteristics and post-event OAC treatment patterns among patients with major GI bleeding.

Methods

Five large national claims databases with the latest available data at the time of application were pooled in this study. They included 100% fee-for-service US Centers for Medicare and Medicaid Services (CMS) data (1 January 2012–31 December 2016), the *Truven MarketScan® Commercial Claims and Encounter* ("*MarketScan*"; 1 January 2012–31 March 2018), the *IMS PharMetrics Plus™ Database* ("*PharMetrics*"; 1 January 2012–30 September 2018), the *Optum Clinformatics™ Data Mart* ("*Optum*"; 1 January 2012–30 June 2018), and the *Humana Research Database* ("*Humana*"; 1 January 2012–30 June 2018).

More details on the datasets can be found in our previous publication.[22] Of note, Medicare supplemental plans in *MarketScan* and *PharMetrics* data were not included in the study to avoid potential duplicates with Medicare Part A and Part B. Details on the pooling method have been published in previous articles.[22,23]

Study design and patient selection

AF patients who were treated with apixaban, dabigatran, edoxaban, rivaroxaban, or warfarin were selected from each database before pooling. The first OAC pharmacy claim date was designated as

the initial OAC prescription date. Patients were required to be ⩾18 years of age in the commercial datasets or ⩾65 years of age in the CMS data and had continuous medical and pharmacy health plan enrollment for ⩾12 months prior to the initial OAC prescription date.

Major GI bleeding events were defined as a hospitalization with a primary diagnosis of GI bleeding during the OAC treatment period. For these patients, the index date was the date of the first major GI bleed hospital discharge date. A control cohort of patients without a major GI bleed during the initial OAC treatment period was created. Selected control cohort patients were randomly assigned hypothetical index dates based on the distribution of the time from initial OAC prescription to index date in the major GI bleeding cohort. The baseline period was defined as 12 months before the index date.

Patients were excluded from the study if they had evidence of valvular heart disease, venous thromboembolism, transient AF (pericarditis, hyperthyroidism, thyrotoxicosis), or heart valve replacement/transplant during the baseline period, pregnancy during the study period, or hip or knee replacement surgery within 6 weeks prior to the initial OAC prescription date. To apply the new-user design, this study limited patients to those without an OAC prescription within 12 months before the initial OAC prescription date.

Among patients with major GI bleed, those who died during the hospitalization were excluded from the study [290/15,224 (1.9%); patients in the *MarketScan* and *PharMetrics* data were not part of this exclusion due to incomplete mortality data]. Furthermore, to evaluate the subsequent effectiveness and safety outcomes post-index date, patients with a follow-up time equal to zero days (minimum follow-up = 1 day) were also excluded.

Outcome measures

For patients with a major GI bleed, time to the event, length of inpatient stay (LOS) for the event, and sites of the major GI bleeding were evaluated, as well as related health care costs and utilization. Treatment patterns during the 90 days after the major GI bleed were also evaluated, including initial OAC re-initiation, discontinuation, and switching (between OACs).

Clinical outcomes were compared between OAC patients who had a major GI bleed and those who did not. Outcomes were evaluated between 1-day post-index date to the earliest of death, end of continuous medical or pharmacy plan enrollment, or the end of study period (follow-up period). Both effectiveness and safety outcomes were studied: for the former, stroke/SE included ischemic stroke, hemorrhagic stroke, and SE; for the latter, major bleeding included GI bleeding, ICH, and major bleeding at other key sites. To ensure mortality data accuracy, all-cause mortality was examined only in CMS data as only the death information from the CMS data is collected and validated from the Social Security Administration.

Statistical methods

The incidence of major GI bleeding was evaluated among all OAC-treated patients. Clinical characteristics and treatment patterns were examined descriptively among patients with a major GI bleed. To compare clinical outcomes of OAC-treated patients with and without a major GI bleed, baseline clinical characteristics of the two cohorts were first evaluated. Propensity score matching (PSM) [1:3 (1 for patients with major GI bleed and 3 for those without)] was conducted within each dataset to adjust for potential confounders and balance the cohorts of interest. A logistic regression model was used to generate propensity scores by predicting the probability of having a major GI bleed among patients in both cohorts.[24] Baseline variables included in the model were patient demographics, index OAC prescription, Charlson comorbidity index (CCI) score,[25] major bleeding (GI bleeding, ICH, and other major bleeding), non-major bleeding, stroke/SE history, comorbidities, co-medications, and inpatient and emergency department visits. By matching the variables listed above, two well-balanced cohorts were created and pooled. Standardized differences with a threshold of 10% were used to denote the statistical and clinical differences between the matched cohorts.[26]

Adjusted comparative clinical outcomes, including stroke/SE, major bleeding, and mortality (in the CMS population), were examined using Cox proportional hazards models with robust sandwich estimates.[22] In addition to the cohort indicator, any post-PSM variables (i.e. baseline major GI bleeding and peptic ulcers) that were

imbalanced were added to the models as independent covariates. All analyses were conducted using SAS 9.4 (Cary, NC, USA).

Institutional review board approval

Since this study did not involve the collection, use, or transmittal of individually identifiable data, it was deemed exempt from institutional review board (IRB) review by Solutions IRB. Both the datasets and the security of the offices where analysis was completed (and where the datasets are kept) meet the requirements of the Health Insurance Portability and Accountability Act of 1996. Solutions IRB determined this study to be EXEMPT from the Office for Human Research Protections (OHRP)'s Regulations for the Protection of Human Subjects (45 CFR 46) under Exemption 4: Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects. The HIPAA Authorization Waiver was granted in accordance with the specifications of 45 CFR 164.512(i). This project was conducted in full accordance with all applicable laws and regulations, and adhered to the project plan that was reviewed by Solutions IRB. Informed consent from subjects included in this study is considered exempt under 45 CFR 46.116(d), which states that the IRB was satisfied that the research presents minimal risk (no risks of harm, considering probability and magnitude, greater than those ordinarily encountered in daily life or during the performance of routine examinations or tests); and the waiver or alteration will not adversely affect the rights and welfare of the subjects; and the research could not practicably be carried out without the waiver or alteration; and whenever appropriate, the subjects will be provided with additional pertinent information after participation.

Results

A total of 848,940 OAC-treated NVAF patients were eligible per the selection criteria, including 15,888 patients with major GI bleeding and 833,052 patients without major GI bleeding (Figure 1).

Major GI bleeding events

After applying the patient selection criteria, among all OAC-treated patients, the incidence rate of major GI bleeding was 2.50 per 100 person-years. After initiation of treatment, the unadjusted incidence rates of the initial major GI bleed were 1.8 (apixaban), 2.2 (dabigatran), 2.0 (edoxaban), 2.8 (rivaroxaban), and 3.0 (warfarin) per 100 person-years. The mean time from the initial OAC prescription to the major GI bleeding event was 78.3 days (median = 40 days; Supplemental material Figure 1 online). For the major GI bleeding events, the mean hospitalization LOS was 4.4 days, with a mean cost of US$11,550; 26%, 24%, and 1% of patients had diagnosis codes for upper, lower, and both upper and lower GI bleeding, respectively. The remaining 49% of patients had diagnosis codes for unspecified GI bleeding. During the hospitalizations for the major GI bleeding events, 40% of patients were admitted to the intensive care unit, 66% had a blood transfusion, and many underwent esophagogastroduodenoscopy (41%) or colonoscopy (18%; Table 1).

OAC treatment patterns after the major GI bleed

For patients with major GI bleeding, 3442 (22%) had apixaban, 822 (5%) had dabigatran, 5065 (32%) had rivaroxaban, and 6542 (41%) had warfarin as the initial treatment (Supplemental Table 1). Within 90 days after the major GI bleed, 58% of patients discontinued the initial OAC treatment. Only 37% of patients re-initiated the same OAC treatment as before the major GI bleed and 5% switched to another OAC. Among patients re-initiating the previous OAC treatment, a small percentage of patients changed to a different dose (5%; Table 1).

Patient characteristics and clinical outcomes

When comparing patient characteristics before PSM, major GI bleeding patients were older and had higher CCI, CHA_2DS_2-VASc, and HAS-BLED scores compared with non-major GI bleeding patients. Patients with major GI bleeding also had a higher percentage of baseline major and non-major bleeding history, comorbidities (such as hypertension, coronary artery disease, and congestive heart failure), and majority of the concomitant medication use (Supplemental Table 1).

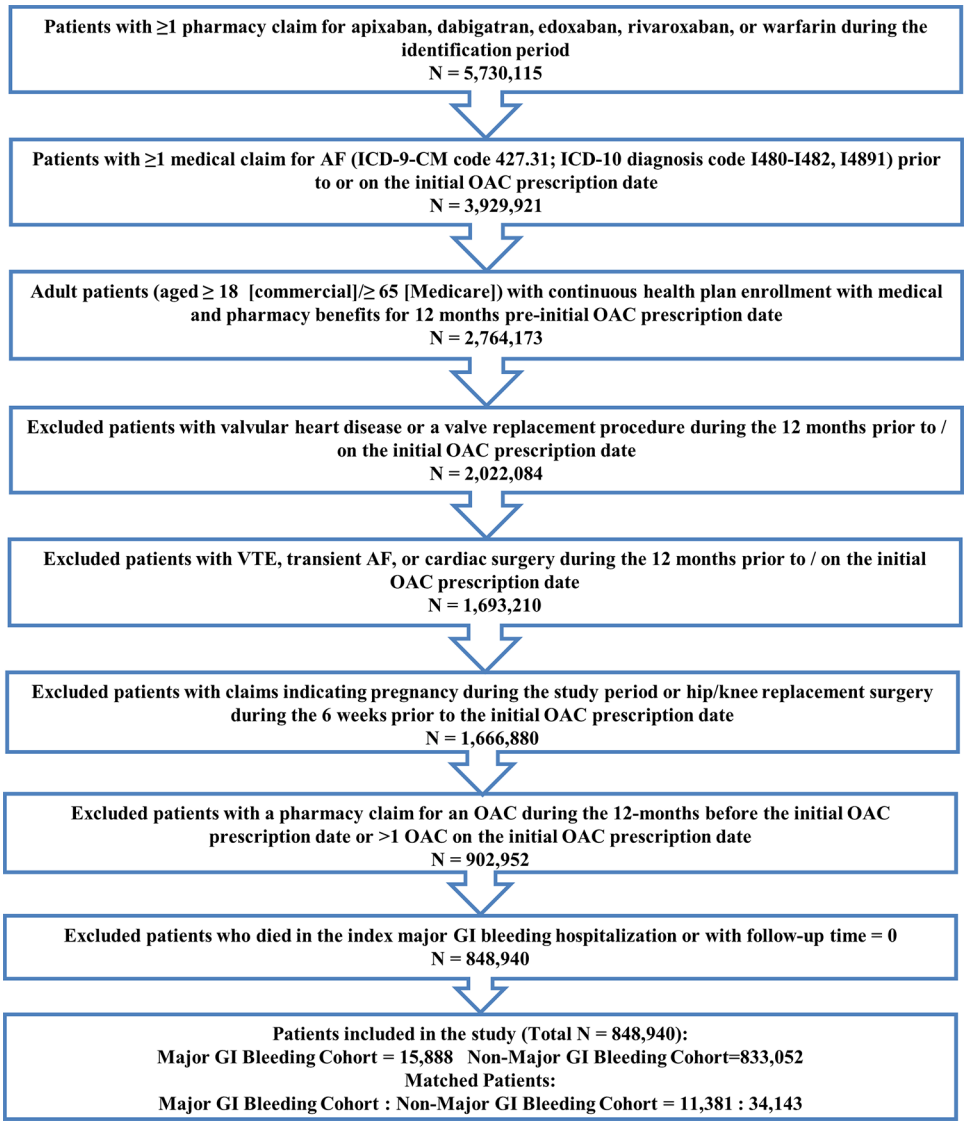

Figure 1. Patient selection criteria.
AF, atrial fibrillation; GI, gastrointestinal; ICD-9/10-CM, International Classification of Diseases – 9th/10th Revision – Clinical Modification; OAC, oral anticoagulant; VTE, venous thromboembolism.

Supplemental Table 2 includes the baseline characteristics of the major GI bleeding cohort stratified by initial treatment type.

The pre-PSM unadjusted incidence rate of stroke/SE was 4.0 for the major GI bleeding cohort and 1.6 for the non-major GI bleeding cohort, and the unadjusted incidence rate of major bleeding was 18.4 for the major GI bleeding and 3.0 for the non-major GI bleeding cohort (per 100 person-years). (Supplemental Table 1).

A total of 34,143 patients without major GI bleeding and 11,381 patients with major GI bleeding were matched with a mean follow-up of 16–17 months (Table 2). Patient characteristics were balanced except for baseline major GI bleeding and peptic ulcers (Tables 2 and 3), which were adjusted for in the Cox proportional hazards models. The cumulative incidence of stroke/SE and major bleeding in the post-PSM population is shown in Kaplan–Meier curves (Figure 2).

After further adjusting for baseline major GI bleeding and peptic ulcers in the Cox models, patients with a major GI bleed had a higher risk of stroke/SE [hazard ratio (HR): 1.57, 95% confidence interval (CI): 1.42–1.74] and major

Table 1. Characteristics of major GI bleeding and treatment patterns after major GI bleeding.

	Patients with major GI bleeding (*N* = 15,888)	
	***n*/mean**	**%/SD**
Major GI bleeding inpatient length of stay (in days)	4.4	7.7
Major GI bleeding inpatient stay costs	$11,550	$15,839
Major GI bleeding site*	15,888	100.0%
Gastroduodenal site	3738	23.5%
Esophageal site	180	1.1%
Upper GI and unspecified upper GI only	4206	26.5%
Lower GI site only	3760	23.7%
Both upper and lower GI sites	114	0.7%
Unspecified GI site	7808	49.1%
Ulcer	1873	11.8%
Perforation	15	0.1%
Selected healthcare resource use	13,523	85.1%
Colonoscopy	2812	17.7%
Esophagogastroduodenoscopy	6522	41.0%
Capsule endoscopy	82	0.5%
Blood transfusion	10,444	65.7%
Fresh-frozen plasma	433	2.7%
Intensive care unit stay	6421	40.4%
Treatment patterns after major GI bleed		
Discontinuation†	9157	57.6%
Switch†	870	5.5%
Days-to-switch	30.9	24.9
Restarting of the same OAC†	5861	36.9%
Days-to-restarting	29.3	22.1
Dose change†,‡	296	5.1%

*The categories for major GI bleeding site are not mutually exclusive.
†Measured within 90 days after the major GI bleed.
‡Among patients that restarted OAC treatment.
GI, gastrointestinal, OAC, oral anticoagulant; SD, standard deviation.

bleeding (HR: 2.79, 95% CI: 2.64–2.95) than patients without a major GI bleed (Figure 3). The associated risk of stroke/SE was mostly driven by ischemic stroke, whereas the risk of major bleeding was mostly driven by GI bleeding.

In the CMS population, the major GI bleeding cohort also had a higher risk of all-cause mortality (HR: 1.29, 95% CI: 1.23–1.36) compared with the non-major GI bleeding cohort (Supplemental Table 3).

Table 2. Baseline demographics, index drug, healthcare utilization, and follow-up time for patients with and without major GI bleeding post propensity score matching.

	Non-major GI bleeding cohort (*N* = 34,143)		Major GI bleeding cohort (*N* = 11,381)		
	***n*/mean**	**%/SD**	***n*/mean**	**%/SD**	**STD**
Age*	78.3	9.0	78.4	9.2	1.7
18–54	319	0.9%	104	0.9%	0.2
55–64	1407	4.1%	529	4.6%	2.6
65–74	9485	27.8%	3178	27.9%	0.3
75–79	7270	21.3%	2417	21.2%	0.1
⩾80	15,662	45.9%	5153	45.3%	1.2
Female*	17,715	51.9%	5796	50.9%	1.9
U.S. geographic region*					
Northeast	6059	17.7%	2022	17.8%	0.1
Midwest	9110	26.7%	3004	26.4%	0.7
South	14,007	41.0%	4691	41.2%	0.4
West	4886	14.3%	1643	14.4%	0.4
Other/unknown	81	0.2%	21	0.2%	1.1
Index drug*					
Apixaban	8037	23.5%	2684	23.6%	0.1
Dabigatran	1703	5.0%	604	5.3%	1.4
Edoxaban	45	0.1%	<11	<0.09%	1.3
Rivaroxaban	10,638	31.2%	3322	29.2%	4.3
Warfarin	13,720	40.2%	4761	41.8%	3.4
Baseline all-cause health care utilization (before index admission/index date)					
Inpatient admission visit*	23,173	67.9%	7982	70.1%	4.9
Outpatient hospital visit	32,503	95.2%	10,831	95.2%	0.1
ER visit*	19,617	57.5%	6607	58.1%	1.2
Office visit	33,762	98.9%	11,222	98.6%	2.5
Pharmacy claim	34,143	100.0%	11,379	100.0%	1.9
Follow-up time (in days)	522.2	429.5	493.6	405.8	6.9
Median	424		397		

*Variables included in the propensity score matching.
ER, emergency room; GI, gastrointestinal; SD, standard deviation; STD, standardized difference.

Table 3. Baseline clinical characteristics for patients with and without major GI bleeding post propensity score matching.

	Non-major GI bleeding cohort (*N* = 34,143)		Major GI bleeding cohort (*N* = 11,381)		
	n/mean	%/SD	*n*/mean	%/SD	STD
Baseline comorbidity					
Charlson comorbidity index*	5.3	3.2	5.4	3.2	2.1
CHA2DS2-VASc score	5.4	1.8	5.4	1.7	0.9
HAS-BLED score	4.3	1.1	4.4	1.0	11.9
History of stroke/SE*	6789	19.9%	2305	20.3%	0.9
Stroke/SE hospitalization	2307	6.8%	782	6.9%	0.5
History of bleeding (before index date/index admission)	15,422	45.2%	5512	48.4%	6.5
Major bleeding hospitalization (before index date/index admission)	2738	8.0%	1295	11.4%	11.4
Major GI bleeding*	1342	3.9%	812	7.1%	14.0
ICH*	151	0.4%	48	0.4%	0.3
Other major bleeding*	1490	4.4%	565	5.0%	2.8
History of non-major bleeding*	12,684	37.1%	4217	37.1%	0.2
Myocardial infarction*	9106	26.7%	3036	26.7%	0.0
Renal disease*	16,462	48.2%	5473	48.1%	0.3
Liver disease*	3772	11.0%	1300	11.4%	1.2
Dyspepsia or stomach discomfort*	13,569	39.7%	4595	40.4%	1.3
Diabetes mellitus*	16,511	48.4%	5557	48.8%	0.9
Hypertension*	32,959	96.5%	11,045	97.0%	2.9
Congestive heart failure*	20,182	59.1%	6602	58.0%	2.2
Non-stroke/SE peripheral vascular disease*	14,466	42.4%	4893	43.0%	1.3
Transient ischemic attack*	5235	15.3%	1771	15.6%	0.6
Anemia and coagulation defects*	31,217	91.4%	10,314	90.6%	2.8
Peripheral artery disease	14,125	41.4%	4811	42.3%	1.8
Coronary artery disease	22,454	65.8%	7691	67.6%	3.8
CABG/PCI	2110	6.2%	723	6.4%	0.7
*Helicobacter pylori**	541	1.6%	191	1.7%	0.7
Diverticulosis*	13,623	39.9%	4413	38.8%	2.3
Peptic ulcers*	4238	12.4%	1812	15.9%	10.1
Ulcerative colitis*	538	1.6%	216	1.9%	2.5
GI cancer (stomach, colon, esophageal, and rectal cancer)*	1239	3.6%	429	3.8%	0.7
Pulmonary disease*	22,568	66.1%	7429	65.3%	1.7
Esophagitis*	3135	9.2%	1205	10.6%	4.7

(Continued)

Table 3. (Continued)

	Non-major GI bleeding cohort (*N* = 34,143)		Major GI bleeding cohort (*N* = 11,381)		
	***n*/mean**	**%/SD**	***n*/mean**	**%/SD**	**STD**
Esophageal varices*	230	0.7%	91	0.8%	1.5
Gastritis*	8961	26.2%	3191	28.0%	4.0
Colonic or rectal ulcer*	140	0.4%	67	0.6%	2.5
Hemorrhoids*	6743	19.7%	2331	20.5%	1.8
Mallory–Weiss syndrome*	93	0.3%	58	0.5%	3.8
Ischemic colitis*	353	1.0%	133	1.2%	1.3
Baseline medication use*					
ACEs/ARBs	22,173	64.9%	7475	65.7%	1.6
Amiodarone	6683	19.6%	2199	19.3%	0.6
Beta blockers	21,834	63.9%	7265	63.8%	0.2
H2-receptor antagonist	3450	10.1%	1172	10.3%	0.6
Proton pump inhibitor	18,156	53.2%	6295	55.3%	4.3
Statins	22,916	67.1%	7655	67.3%	0.3
Antiplatelets	9109	26.7%	3113	27.4%	1.5
NSAIDs	7104	20.8%	2410	21.2%	0.9
Inhibitors of warfarin	29,521	86.5%	9849	86.5%	0.2
Inducers of warfarin	16,315	47.8%	5531	48.6%	1.6
Dronedarone	1191	3.5%	346	3.0%	2.5
Digoxin	4778	14.0%	1544	13.6%	1.2
Calcium channel blockers	17,470	51.2%	5887	51.7%	1.1
Renin–angiotensin system antagonists	22,954	67.2%	7732	67.9%	1.5
Glucocorticoids	19,017	55.7%	6348	55.8%	0.2
Diuretics	23,595	69.1%	7868	69.1%	0.1
Metformin	6320	18.5%	2125	18.7%	0.4
Sulfonylureas	4351	12.7%	1415	12.4%	0.9
Thiazolidinedione	676	2.0%	233	2.0%	0.5
Insulin	5303	15.5%	1799	15.8%	0.8
Other diabetes drugs	2387	7.0%	796	7.0%	0.0
Antiulcer agents	17,507	51.3%	6064	53.3%	4.0
Antidepressant	11,791	34.5%	4005	35.2%	1.4

*Variables included in the propensity score matching.
ACE/ARB, angiotensin converting enzyme inhibitor/angiotensin-receptor blocker; CABG/PCI, coronary artery bypass grafting/percutaneous coronary intervention; GI, gastrointestinal; ICH, intracranial hemorrhage; NSAID, non-steroidal anti-inflammatory drug; SD, standard deviation; SE, systemic embolism; STD, standardized difference.

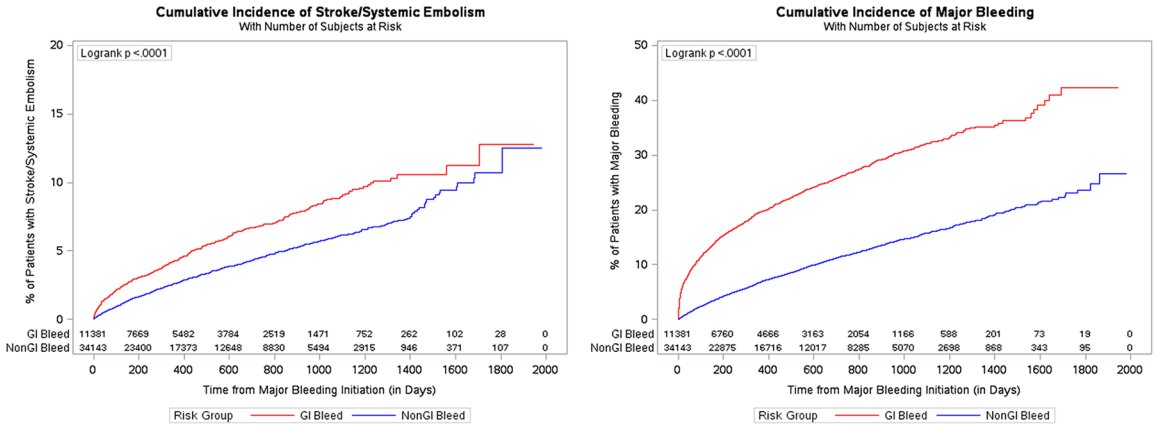

Figure 2. Kaplan–Meier curves for stroke/systemic embolism and major bleeding for patients with and without major GI bleeding in the propensity score matched population.
GI, gastrointestinal.

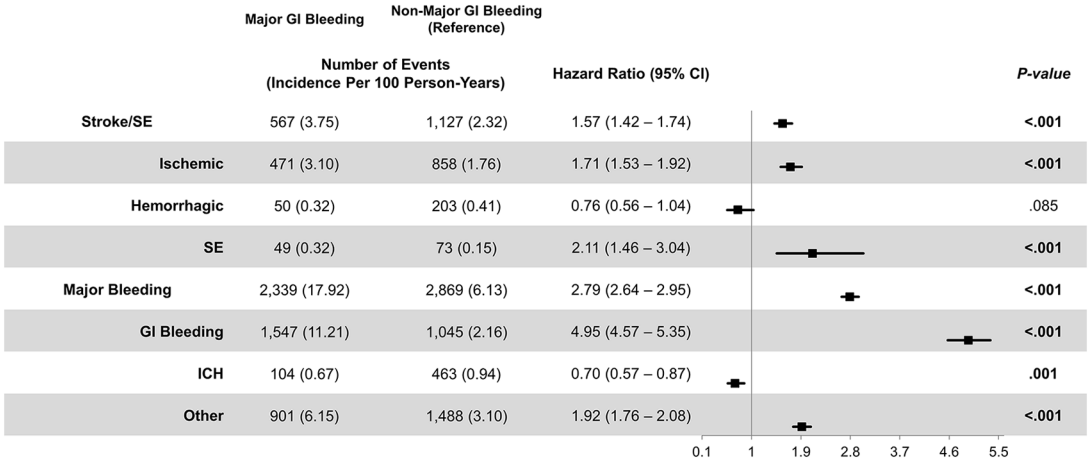

Figure 3. Propensity score matched incidence rates and hazard ratios of stroke/SE and major bleeding for patients with and without major GI bleeding.
Note. Major GI bleeding and peptic ulcers were included as covariates in the Cox proportional hazards models as they were unbalanced after propensity score matching.
CI, confidence interval; GI, gastrointestinal; ICH, intracranial hemorrhage; SE, systemic embolism.

Discussion

This study analyzed pooled data from five US national claims datasets, including both Medicare enrollees and the commercially insured. To our best knowledge, it is the largest real-world study to assess the characteristics and consequence of major GI bleeding events and subsequent treatment patterns among OAC-treated NVAF patients. Over half of patients with a major GI bleed discontinued OAC treatment within 90 days after hospital discharge from the event. Second, when compared with OAC-treated patients without a major GI bleed, those with a major GI bleed had a significantly higher risk of subsequent stroke/SE and of major bleeding after hospital discharge. The risk of mortality was also higher for patients with a major GI bleed in the CMS population.

In the pivotal RCTs for NOACs and warfarin among AF patients, GI bleeding was the most prevalent type of major bleeding after OAC treatment: among the enrolled NOAC treated patients, 3.6–6.2% had overall major bleeding and 1.2–3.2% had major GI bleeding.[10–12,27] Various real-world studies have also examined the risk of GI bleeding among OAC-treated NVAF patients, with findings regarding prevalence of GI bleeding

and comparative risk that are generally consistent with the abovementioned RCTs.[28,29] Similarly, in our study, 1.9% (15,888) of selected NVAF patients (N = 848,940) had a major GI bleed.

Despite the clinical evidence and ESC guidelines,[22] more than half of the patients in our study were found to have discontinued their OAC treatment after a major GI bleed. Similar to our findings, Hernandez *et al.*[30] reported a less than 50% re-initiation rate of OACs after a major hemorrhage in the Medicare population from 2010 to 2012. However, in multiple studies OAC re-initiation has been found to be associated with a lower risk of stroke and all-cause mortality than OAC discontinuation.[30–33] Furthermore, two meta-analyses concluded that among OAC-treated NVAF patients with a major bleed, restarting OAC therapy afterwards was associated with a reduced risk of stroke and mortality without increasing the risk of subsequent bleeding.[33,34] While our study did not evaluate the impact of restarting OACs on subsequent events after the major GI bleed, the higher stroke/SE risk may be related to the high OAC discontinuation rate after the index major GI bleeding event. The higher subsequent risk for both stroke/SE and major bleeding among those with an index major GI bleed compared with those without indicates serious consequences of a major GI bleed. These findings also raise the importance of evaluating the risk of stroke/SE and bleeding associated with OAC treatments and of restarting OACs among patients with a major GI bleed.

The importance of minimizing major GI bleeding among OAC-treated NVAF patients warrants further study in this area. This study leveraged data from five large, nationally-representative insured populations to examine relevant real-world associations regarding OAC treatment and major GI bleeding. The study's analysis of clinical characteristics, treatment patterns, and follow-up risk of stroke/SE and major bleeding provides an overall picture about the burden of major GI bleeding and current clinical practice patterns after a major GI bleeding among OAC-treated NVAF patients. Moreover, given that major GI bleeding is the most common type of bleeding among OAC-treated NVAF patients, the information regarding clinical characteristics and associated comparative subsequent risk of stroke/SE and major bleeding may be important for AF management decision-making.

Limitations

Despite its novelty and sufficient statistical power, this study has several limitations. For instance, the observational retrospective study design is limited to observation of associations as opposed to inference of causal relationships. Although PSM was conducted to adjust for a comprehensive list of covariates when comparing patients with and without major GI bleeding, some residual confounding is still expected.

Additionally, the use of insurance claims data may have introduced bias into the study. For example, information on drug administration in the inpatient setting is unavailable in claims data, so only outpatient prescription information was available for treatment pattern analysis. Hence, patients who opted out of treatment or extended the drug use prior to or after the index hospitalization may have been misclassified. Similarly, prescription claims cannot capture information on whether the medication was administered as prescribed or at all and claims data cannot capture certain clinical parameters. Claims data may also have coding errors and lack clinical adjudication, resulting in inaccurate diagnoses or procedure codes that were used to measure the outcomes. Finally, the results may not be generalizable to the overall NVAF population in the United States because the study did not include uninsured patients or patients solely covered by public health insurance plans other than the Medicare.

Conclusion

OAC-treated NVAF patients who had a major GI bleeding event were more likely to develop recurrent major bleeding and subsequent stroke/SE compared with those without a major GI bleed. Over 50% of patients discontinued their OAC within 90 days after discharge from hospitalization for a major GI bleed; therefore, future analysis is needed to determine the impact of treatment discontinuation on clinical outcomes. Given the serious consequences of major GI bleeding among OAC-treated NVAF patients, more research is needed to identify effective management strategies for these high-risk patients that can minimize major GI bleeding in this patient population.

Conflict of interest statement

S Deitelzweig is a consultant for Bristol Myers Squibb Company/Pfizer Inc., Daiichi-Sankyo,

Portola, and Boehringer Ingelheim, and has been on the speakers' bureau for Bristol Myers Squibb Company/Pfizer Inc., and Boehringer Ingelheim.

A Keshishian is a paid employee of STATinMED Research which is a paid consultant to Pfizer Inc. and Bristol-Myers Squibb Company.

A Kang, A Dhamane, N Balachander, L Rosenblatt, and J Jiang are paid employees and shareholders of Bristol-Myers Squibb Company.

X Luo and J Mardekian are paid employees and shareholders of Pfizer, Inc.

GYH Lip is a consultant for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. No fees are directly received personally.

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ORCID iD

Allison Keshishian https://orcid.org/0000-0002-9986-1227

Supplemental material

Supplemental material for this article is available online.

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